Clinical and laboratory-based methods in the diagnosis of natural rubber latex allergy

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The accurate diagnosis of hypersensitivity to natural rubber latex is the initial step in the effective management of individuals with latex allergy and in ensuring the quality of epidemiologic studies. The diagnostic algorithm used in the evaluation of an individual with suspected latex allergy begins with a comprehensive clinical history during which risk factors (atopy, food allergies, hand dermatitis) and temporal relationships between symptoms and natural rubber product exposure are identified. If type IV hypersensitivity is suspected because of the delayed nature (hours to days) and confinement of symptoms to the skin-latex product contact areas, patch testing can be conducted to confirm the presence of activated T cells with specificity for rubber chemicals. If type I hypersensitivity is suspected because of ocular, upper and lower airway, and/or systemic symptoms that have rapid onset (minutes) after a definable latex exposure, a confirmatory skin or blood test for IgE antibody may be conducted to verify a state of sensitization within the individual. The definitive diagnosis would then be made only after consideration of the individual's clinical history and confirmatory in vivo and/or in vitro laboratory test results. If discordance remains between highly convincing latex-associated symptoms as identified in the history and repetitively negative confirmatory IgE antibody test results, then one of several types of in vivo provocation tests may be performed for adjudication. This overview examines the current state of the art in both in vivo and in vitro diagnostic methods for latex-specific IgE antibody detection in skin and blood. The performance, advantages, and limitations of each diagnostic method are compared. (J Allergy Clin Immunol 2002;110:S47-56.)

Key words: *Natural rubber latex, hypersensitivity, skin tests, latex-specific IgE antibody*

Immediate-type hypersensitivity to natural rubber latex (NRL) has emerged during the last 2 decades of the 20th century as a recognized public health concern. Clinical and basic scientists, in an attempt to determine the magnitude of the latex allergy problem, have performed numerous epidemiologic studies to define the prevalence of latex allergy in the general population and suspected high-risk groups. These studies have also focused on identifying risk factors and defining time-related trends in the incidence or emergence of new cases. At the core of these epidemiologic study predictions has been the need to diagnose "true" cases of latex allergy. Thus, the issue of accurate diagnosis has been of foremost importance because it has not only determined the accuracy of incidence and prevalence statistics but also determined the ability of physicians to identify and treat latex-sensitive individuals in clinics throughout the world.

Historically, a number of clinical and laboratory-based methods have been used to diagnose human allergic disease.[1,2] Skin and serologic tests have been most commonly used to confirm a history consistent with allergy to any of over 100 known allergenic substances from biologic sources including weeds, grasses, trees, pet dander, dust mites, foods, and molds. Over the past decade, the development of NRL–specific diagnostic reagents for use in skin and blood testing has consumed much effort. Although the quality of well-characterized latex reagents has been improving, there is still room for improvement. This article provides an overview of the historical evolution of a general diagnostic algorithm for NRL allergy and the current status of latex reagents and methods used in the diagnostic workup of individuals with suspected latex allergy.

DIAGNOSTIC ALGORITHM

By the time of the first international symposium on latex allergy in 1992, in vivo and in vitro diagnostic reagents for detecting latex-specific IgE antibody in human blood and skin were only available in research centers throughout North America and Europe. Finnish inves-

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Abbreviations used
AL: Ammoniated latex
FDA: Food and Drug Administration
IDST: Intradermal skin test
NAL: Nonammoniated latex
NRL: Natural rubber latex
SPT: Skin prick test

tigators had reported success with diagnostic T-cell proliferation assays, basophil histamine release, immunoblotting assays for IgE antibody, and skin prick tests (SPTs) with latex glove extracts.[3-5] In the United States, reports by Kelly et al[6,7] in 1993 and 1994 described the diagnostic algorithm, considered optimal at that time, for assessment of latex allergy. Once a patient had been identified as being at risk for latex allergy on the basis of a thorough clinical history, he or she was evaluated by serology, a provocation glove use test, and an SPT, in that order. Skin prick testing had been placed last in the diagnostic algorithm pecking order because of a general concern for patient safety, since adverse systemic reactions had been reported after SPTs with latex glove extracts.[6] In the 1993 study, 118 patients including 85 children with spina bifida, 15 health care workers, and 6 others with symptoms of latex allergy and 10 control subjects were evaluated for latex-specific IgE antibody. Systemic reactions (anaphylaxis with hypotension, hives, angioedema, and/or wheezing) were reported in 9 of 107 patients and 0 of 10 control subjects who underwent SPTs with a 24-hour phosphate-buffered saline extract of powdered latex medical gloves administered with a multitest puncture device (Lincoln Diagnostics, Decatur, Ill). One patient experienced anaphylaxis with hypotension and hives in response to a 1:100,000 dilution of the latex glove extract. The 8.4% frequency of severe adverse reactions associated with SPTs with latex allergen extracted from powdered latex rubber gloves contrasted with historical data in which a 0.04% to 1.4% frequency of severe adverse reactions (asthma and anaphylaxis) had been reported for SPTs with other allergens.[8-10]

More recently, the availability of standardized latex skin testing reagents in Canada and Europe has allowed clinicians and researchers to gain confidence that the SPT with latex is an inherently safe procedure, with a low risk of inducing systemic allergic reactions. The currently accepted diagnostic algorithm for latex allergy is shown in Fig 1. It involves obtaining an initial thorough clinical history, which is followed by a diagnostic skin test (when a standardized reagent is available), a serologic test for latex-specific IgE antibody with a Food and Drug Administration (FDA)–cleared method, and lastly, in vivo provocation testing.

CLINICAL HISTORY

Obtaining a comprehensive clinical history is the initial step in the diagnostic process for any suspected type I hypersensitivity reaction to NRL. An individual may present with complaints of a spectrum of allergic symptoms that he or she believes are temporally associated with NRL product use or exposure. In medical and nursing home environments, for instance, powdered latex medical gloves are considered an important source of latex allergen exposure.[11,12] Although the cornstarch donning powder in powdered latex gloves is not considered allergenic, it is considered a carrier for some latex allergens.[13] Some individuals, once sensitized, may remain free of symptoms until further latex allergen exposure leads to overt skin, ocular, and upper and lower airway allergic symptoms. The temporal association between latex exposure and allergic symptoms may be strengthened by the disappearance and reappearance of allergic symptoms after concurrent separation from and reintroduction of the individual to a known latex allergen source.

A number of questions similar to those used in a multicenter latex skin testing study[14] can be useful in determining whether an individual's clinical history is consistent with the diagnosis of latex allergy. First, the individual's general atopic history (seasonal rhinitis, early-onset asthma, eczema, food allergy) should be obtained because atopy, hand dermatitis, and allergies to certain foods are known risk factors associated with latex allergy. Second, occupational information helps identify repetitive uses of natural rubber products, which can increase the individual's frequency and magnitude of latex allergen exposure. Third, the individual should be asked about the time course and magnitude of any localized or systemic allergic symptoms (skin, eyes, upper and lower airways) that might be associated with latex exposure. Reports of dermatitis, swelling, redness, and irritation confined to the area of skin-rubber contact are particularly useful in discriminating between individuals with type IV and type I hypersensitivity. Information about the frequency and type of reactions to latex and the number of surgeries the individual has had with general anesthesia aid in determining a positive latex allergy history.

For individuals who exclusively report skin symptoms, the time course and extent to which these symptoms are confined to the area of latex-skin contact may lead the diagnostician to suspect a delayed-type (type IV) hypersensitivity. Once the suspicion of IgE antibody-mediated latex allergy is made probable by the history, one of several IgE antibody confirmatory tests can be used to support this diagnosis by identifying a state of sensitization to latex allergen. Only a subset of individuals who become sensitized to latex, as evidenced by latex-specific IgE antibody in their blood or skin, will exhibit overt symptoms after latex allergen exposure.[15] The relationship between sensitization (IgE anti-latex positivity) and being allergic to latex (manifesting allergic symptoms on latex allergen exposure) depends on the extent of sensitization (frequency and magnitude of latex-specific IgE antibody in the skin and/or blood), the heterogeneity of the IgE antibody specificity for the individual *Hevea* allergens, and the magnitude of personal latex allergen exposure.

CONFIRMATORY DIAGNOSTIC TESTS

Two confirmatory tests have been extensively used to detect the presence of latex-specific IgE antibody in the skin or blood of an individual. The skin test is an attractive test used by allergists because it is rapid and sensitive, and it involves a clinically observable biologic (wheal and erythema) response on the skin of the individual. However, many variables influence the accuracy of the skin test, the most important of which is the composition and potency of skin test extracts (Table I). Because there are currently no FDA-approved latex skin test extracts, serologic tests for latex-specific IgE have become important diagnostic latex allergy confirmatory tests in the United States. Lastly, in vivo provocation tests may be used to adjudicate the diagnostic status of individuals with a positive history who have a negative skin test or serologic test result for latex-specific IgE. Each of these tests is discussed in relationship to safety, performance, and strengths versus limitations.

SKIN TESTING

In the early to mid-1990s, extracts prepared from powdered NRL medical gloves, and occasionally, crude latex preparations directly from *Hevea brasiliensis trees*[4,6,7] were used as reagents for diagnostic skin testing. Difficulty in the interpretation of results from these SPTs stemmed from the fact that the glove extracts being used were not uniform, quality control was poor, and the allergenic content and stability of the extracts were unknown. Variability in the allergen content among extracts of gloves raised concerns about the consistency of their diagnostic performance and safety.[6]

Phase I/II clinical study

After the 1992 International Latex Allergy Symposium, a systematic plan for development of a latex skin testing material was initiated with the ultimate goal of establishing an FDA-licensed extract for use in the United States. An initial phase I/II clinical study was conducted to determine the relative safety and diagnostic accuracy (sensitivity and specificity) of 3 candidate latex source materials: nonammoniated latex (NAL), ammoniated latex (AL), and extracts of powdered latex gloves.[16] In the study, 102 adults with either a positive (n = 78) or negative (n = 24) history of adverse reactions to NRL gloves were recruited, and informed consent was obtained. Nineteen of the 78 subjects with a positive history were classified as having type IV hypersensitivity as a result of reporting a rash, pruritus, and/or irritation confined to their hands after hours of wearing gloves. Each subject provided blood and underwent multiple skin tests with 1 to 1000 μg/mL (SPT) and 1 pg/mL to 1 μg/mL (intradermal skin test [IDST]) of NAL, AL, and glove extract. An IgE anti-latex RAST and 2-stage latex/vinyl glove use provocation test were subsequently performed to assist in clarifying the latex allergy status of 9 of the 59 subjects who were classified, on the basis of history, as having type 1 hypersensitivity to latex but who had negative SPT and IDST responses.

This study showed an absence of systemic or large local allergic reactions with either SPTs or IDSTs, which supported the safety of latex skin testing with any of the 3 extracts. After normalization to 1 mg/mL total protein, all 3 latex sources (glove extract, NAL, and AL) displayed equivalent diagnostic performance (sensitivity and specificity) when tested as SPT and IDST reagents at

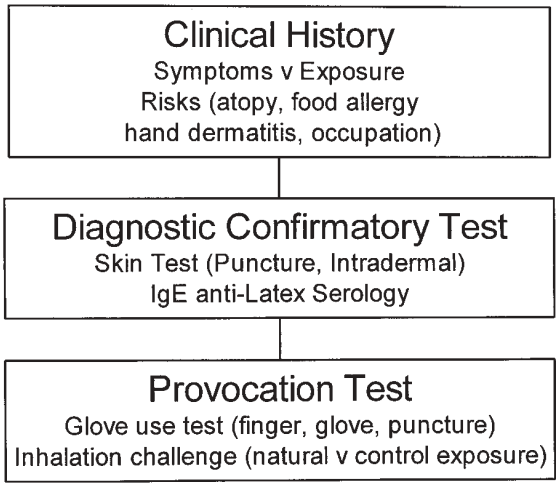

FIG 1. The currently used diagnostic algorithm for latex allergy assessment involves an initial clinical history, secondary confirmatory test (skin test and/or IgE anti-latex serologic test), and lastly, and in vivo provocation test. The pros and cons of each aspect of this diagnostic algorithm are described in the text.

TABLE I. Latex skin test variables and reagent sources

Potential source materials	Medical powdered latex gloves, NAL, low vs high AL
Optimal composition	Hev b 1, 3, ENSP on rubber particle or lutoids, Hev b 2, 4, 5, 6, 7, 8, 9, 10, 11 in C-serum
Inter-lot variability	*Hevea brasiliensis* tree clone seasonal variation in protein content
Manufacturing methods	Agitation, extraction buffers, centrifugation conditions
Quality control assays	ELISA or RAST inhibition, SDS-PAGE, Western blot analysis with identity markers
Commercial sources	Glove extracts: in-house[3-7,11,20]
Latex extracts	Bencard reagent: AL, unprocessed latex[17,18]
	Stallergenes reagent (approved in Europe): NAL, C-serum[19,20]
	Investigational Greer reagent: NAL, C-serum[14]
	Investigational Diagnostic Products Corp: NAL[19]
	ALK-Abello: C-serum
	FDA, E8-FDA: NAL, C-serum

NAL, Nonammoniated latex; *SDS-PAGE,* sodium dodecylsulfate–polyacrylamide gel electrophoresis; *FDA,* Food and Drug Administration; ENSP, early nodule specific protein.

the various extract concentrations. However, of the 3 source materials, NAL was identified as having the most potential for further development into a skin test reagent because it displayed the most reproducible inter-batch potency in quality control RAST inhibition tests.[16] The potency of AL and glove extracts appeared to vary between batches. This variability in potency was believed to be due to variability in protein composition of the starting material and storage-dependent protein degradation. NAL also produced clear banding patterns on sodium dodecylsulfate–polyacrylamide gel electrophoresis and Western blot analysis, which were more easy to interpret than the smeared patterns of the AL and glove extracts. Because AL is used in the manufacturing of dipped and molded rubber products, a recurring concern has been that the allergenic proteins in NAL might not be structurally identical to those in AL. This raises the possibility that they therefore might be less "diagnostically" relevant than those in the ammoniated form of *H brasiliensis* latex. To date, there is no direct evidence that NAL skin testing reagents systematically fail to detect latex-specific IgE antibody that is detectable with AL in the skin of subjects with latex allergy.

In terms of diagnostic performance, optimal sensitivity and specificity for all 3 latex source materials were achieved at 100 μg protein/mL for SPTs and 1 μg protein/mL for IDSTs. Of special note, 9 of the 59 subjects with a positive type I hypersensitivity history had negative skin test responses to all 3 extracts, and 8 of these 9 subjects had a negative latex–anti-IgE serologic test result. Only 5 of these 9 subjects were available to undergo a 2-stage glove provocation test (discussed below), and all results of these challenge tests were negative. The negative provocation test results support the conclusion that the positive history of latex allergy in these 5 subjects with negative skin test responses was most probably a false-positive history. Because of the questionable positive histories, skin test data from these 5 subjects were initially excluded from the analysis in which the performance of the 3 skin test materials was compared. The reason for exclusion stemmed from a belief that only data from subjects who had clear positive and negative histories should be used to compare the performance of the 3 skin test materials. This produced a 93% to 96% diagnostic sensitivity and 96% to 100% diagnostic specificity for NAL in IDSTs and SPTs.[16] Subsequent analysis, in which skin test results for these 5 subjects with a positive history were included as false-negative results, reduced the diagnostic sensitivity for all 3 extracts to approximately 85%. The principal conclusions of the study remain the same whether these 5 cases were included or excluded from the analysis. The conclusions were (1) both SPTs and IDSTs with latex are inherently safe when the protein concentration is monitored, (2) all 3 latex source materials (NAL, AL, and glove extracts) produce comparable diagnostic skin test results when normalized for protein concentration, and (3) NAL is the most attractive candidate latex for further development because of its stability and ease of quality control.

Multicenter phase III clinical study

A multicenter clinical study was conducted to confirm the safety and assess the diagnostic sensitivity and specificity of a candidate *H brasiliensis* NAL extract produced by a licensed allergen manufacturer (Greer Laboratories, Lenoir, NC) by using the 1994 study[16] formulation. In the multicenter study,[14] 324 subjects met the inclusion criteria and were classified by their clinical history as being latex-allergic (124 adults and 10 children) or non–latex-allergic (180 adults and 10 children). Subjects provided a blood sample for latex-specific IgE testing. Each then underwent sequential SPTs with Malaysian NAL (Greer Laboratories) at latex protein concentrations of 1, 100, and 1000 μg/mL administered with a bifurcated needle.

The FDA review panel initially agreed that a 2-stage glove provocation test (see below) should be used to clarify the latex allergy status of individuals with a positive latex allergy history but a discordant negative SPT response, or alternatively, a negative history and a discordant positive SPT response. In this study, 24 subjects (15%), originally designated as latex- allergic on the basis of their clinical history, were reclassified to the non–latex-allergic group on the basis of a negative glove provocation test result. Of the 134 subjects classified as latex-allergic, 54 (40%) had positive SPT responses to NAL (1 μg/mL) and were deemed to be highly sensitive. In terms of safety, only mild reactions (mainly pruritus) were recorded in 15.1% of adults with latex allergy and 4.4% of adults not allergic to latex. No reactions that required treatment with epinephrine occurred as a result of skin testing, supporting the safety of the NAL SPT reagent. The published diagnostic sensitivity (95%) and specificity (100%) of the Greer SPT reagent at the 100 μg/mL concentration has been attributed by some critics to the use of a glove provocation test to reassign the history status of some study subjects (eg, those with a positive history and negative skin test results).

The multicenter skin testing study data were reanalyzed by an impartial allergist (D.O.), who reviewed all the original case reports and used the initial clinical history as the reference for assigning subject latex allergy status, to address concerns about potential bias of case assignment and data analysis. A biostatistician (E.P.) then analyzed the multicenter study data using "intent to diagnose" and "according to protocol" statistics. This was done both excluding cases defined as "contact dermatitis" and including these contact dermatitis cases with reported type IV hypersensitivity as latex allergy or type I hypersensitivity–negative. The overall sensitivity of the Greer NAL SPT reagent changed from 95% when the glove provocation challenge was used as the qualifier for reassigning the latex allergy history to 70% to 75% (95% CI, 65-83) when the original clinical history alone was used to define the latex allergy status of subjects. The diagnostic specificity of the Greer NAL reagent remained essentially unchanged at 97% to 99%, whether the initial or revised history was used to define the latex allergy status of the subject.

Other studies

Although several other in vivo studies of latex skin test extract performance have been done, no one study seems to stand out as definitively conclusive.

In 1995 and 1996, Hadjiliadis et al[17] performed skin tests using the Bencard latex reagent, which is unprocessed *H brasiliensis* AL produced in Canada. Defining the SPT response as 2+ positive if the wheal was 3 to 5 mm greater than the negative control response at 10 minutes, they identified a 4.2% prevalence of positive latex skin test responses among hospitalized patients in an asthma and allergy practice.[17] The following year, they showed a positive association between the size of the SPT response and the severity of the latex-induced symptoms in 47 patients with positive skin test responses.[18] The authors suggested that knowledge of the clinical severity of symptoms may aid in ensuring a safe starting dilution of latex for skin prick testing to prevent any systemic reactions.

In 1997, Ebo et al[19] reaffirmed the safety of SPTs by using an investigational NAL in their comparative study of IgE antibody detection methods. They performed SPT titration from 10^{-3} to 1 μg/mL and detected positive SPT responses with wheal diameters >3 mm in 68% of history-positive patients. The addition of an IDST titration from 10^{-6} to 10^{-3} μg/mL increased the diagnostic sensitivity of their skin test procedure to 97%. No adverse systemic reactions associated with skin testing were reported. However, their report provides no immunochemical quality control data or comparative data with any of the other skin testing reagents noted in Table I. Because their study was not performed with an NAL skin test reagent using an approved FDA protocol, their reagent was not considered a potential candidate for FDA licensure.

In Europe, Turjanmaa et al[20] examined the diagnostic performance of an NAL SPT reagent manufactured by Stallergenes in Fresnes, France. In their 1997 study, 46 subjects with latex allergy and 76 nonallergic control subjects were enrolled on the basis of their history and underwent SPTs with the Stallergenes NAL reagent; an index of reactivity of 100 (22 μg protein/mL) was used. They reported a diagnostic sensitivity of 93% and a specificity of 100% for the Stallergenes reagent. Moreover, Western blot analysis banding patterns observed at 14, 20, 27, 30, and 45 kd with the Stallergenes latex reagent corresponded to known IgE-binding proteins also detectable in the FDA's E8 NAL reference material. The method of NAL collection and available in vitro quality control data for the Greer and Stallergenes reagents appear to be comparable. Depending on how latex allergy cases are defined (see phase III study above), their clinical performance data may also be considered comparable.

Also in Europe, Vandeplas et al[21] evaluated the diagnostic performance of the Stallergenes NAL SPT reagent in 45 consecutive patients who were referred for treatment of suspected latex-related occupational asthma. A history was obtained by using an open medical questionnaire, and inhalation challenges were performed with powdered latex gloves and spirometry. Using the latex glove inhalation provocation challenge as the reference or diagnostic standard for defining latex-induced asthma, the authors showed that the clinical history and SPT results displayed a high diagnostic sensitivity (87% and 100%, respectively) but a low diagnostic specificity (14% and 21%, respectively). A physician using a standardized questionnaire first obtained the clinical history. It is noteworthy that the history was then masked and re-graded by 3 other physicians with respect to the likelihood of occupational asthma related to latex. The level of agreement among the 4 physicians (2 chest physicians and 2 occupational health physicians) in the interpretation of the clinical history was poor, with concordances ranging from 17% to 59%. Even when this "consensus" history was used as the reference method, there was only modest agreement with the results of different diagnostic tests. Combining results of the SPT and history improved the negative predictive value from 50% to 71%, whereas the positive predictive value remained virtually unchanged (75%-76%).

At present, allergists in the United States who wish to perform diagnostic skin testing are forced to prepare their own in-house latex extracts from powdered latex gloves because there is no other option. Occasionally, a glove extract that has been subjected to a diagnostic performance evaluation is available in a limited quantity.[22] However, the majority of the glove extracts used by allergists are prepared as a 15- to 30-minute extract of a glove just before skin testing, and no quality control testing is performed. Use of these extracts and interpretation of resultant skin reactions are ill-advised, and the practice may even be dangerous. Concerns are related to the unknown diagnostic accuracy and safety of in-house uncharacterized latex glove extracts. A standardized latex skin testing reagent will eventually be licensed by the FDA for use in the United States.

SEROLOGIC TESTING

The first extensive discussion of serologic assays for latex-specific IgE antibody occurred at the International Latex Conference on Sensitivity to Latex Products in Medical Devices in 1992. Three groups[23-25] reported on their research in which the RAST-type assay was used as the prototype format. A variety of latex allergen preparations from gloves and centrifuged ammoniated and nonammoniated *H brasiliensis* latex were initially coupled to different solid phases (microtiter plates, agarose, and cellulose particles) to prepare an allergosorbent. Human serum was then added, and if latex-specific IgE was present, it bound to the insolubilized latex allergens. After a washing step, latex-bound IgE antibody was detected with a labeled anti-human IgE. The response signal obtained in the final assay step (eg, counts per minute bound, optical density, fluorescence) was proportional to the amount of latex-specific IgE antibody bound.

Research assays

The first challenge was to identify the ideal diagnostic latex allergen source for in vitro use. Several laboratories

developed a panel of RAST-type assays for latex-specific IgE antibody by using an in-house glove extract, AL, and NAL.[23,26,27] In 1994, we compared the performance of a RAST assay that used 3 potential latex allergen sources.[26] NAL, AL, and powdered latex glove extracts were prepared and coupled to carbohydrate particles. NAL was collected from the *H brasiliensis* tree and mixed 1 part to 2 parts of nondenaturing preservative (50% wt/vol glycerol, 3 mmol/L cysteine, 0.1 mol/L sodium bicarbonate, and 0.1 mol/L sodium azide). The AL was collected into either 0.15% (low) or 1.6% (high) ammonia instead of the nondenaturing preservative. On ultracentrifugation, both these latex preparations formed 3 layers: a white cream top button that contained virtually all the isoprene polymer, a translucent central fluid (C-serum) with solublized proteins that was used for coupling to the solid phase, and a pelleted bottom layer containing organelles (lutoids). Extracts were also prepared from powdered latex examination gloves by adding 5 mL of phosphate-buffered saline solution per gram of glove and rotating the mixture for 16 hours at 23°C.

We hypothesized that the latex glove and possibly the AL preparations might contain the most relevant populations of allergenic proteins because these represent the primary sources of latex allergen from which exposure occurs. To our surprise, we observed good concordance in the frequency of positive latex-specific IgE antibody results as measured in RAST-type assays when different glove, AL, and NAL extracts were insolubilized and used in assays in a blinded study at 2 universities.[26] The latex glove extracts produced assays with sensitivities that were equivalent to or slightly better than those that used NAL. As discussed with regard to skin testing reagents, the NAL exhibited more uniformity between batches and was easier to control for quality with immunoblotting methods. Concern over the variability of allergenic proteins extracted from gloves and the anticipated progressive cleavage of latex proteins in ammonia discouraged the use of AL and glove extracts over NAL in the preparation of latex allergosorbents. The prototype RAST assay with NAL displayed an interassay coefficient of variation <20% and analytical sensitivity of 0.6 ng/mL.[26] These early assays were able to detect latex-specific IgE antibody from 0.7 to 338 ng/mL in the serum of two thirds of the systemic reactor group (n = 33) who manifested respiratory symptoms with and without anaphylaxis after latex exposure. Latex-specific IgE was also detected in the serum of 1 of the 10 latex-exposed clinically non-latex-allergic control subjects, suggesting a 90% diagnostic specificity.

At approximately the same time, Kurup et al[27] reported on an ELISA that used 2 glove extracts and 2 AL preparations from Malaysia and India on their allergosorbents. They evaluated sera from both clinically latex-sensitive subjects (n = 45) and nonsensitized control subjects (n = 27). Considerable differences in reactivity of IgE antibody from patients with latex allergy were observed with the different antigens. Sera from 50% of Finnish and 72% of American patients with clinical evidence of latex allergy contained detectable IgE antibody as determined with these assays. This is in contrast to the finding of positive IgE anti-latex serology in 7.4% of clinically non–latex-allergic control subjects.

Jaeger et al[28] prepared a disk of latex that was punched directly from a latex glove. Their intent was to enhance analytical performance of the IgE anti-latex RAST by using a solid-phase latex allergen that reflected the actual latex allergen source (the glove) believed to be involved in contact and inhalation exposure. Although this was a novel idea, use of the glove disk did not improve assay sensitivity. In fact, variable nonspecific binding on the glove disk occurred, and binding was erratic because gloves exhibit variable allergen potency.

At the time of these early RAST-type research assays for latex-specific IgE antibody, there were no FDA-cleared assays on the horizon. Diagnostic and analytical performance was documented by using sera from studies in which subjects had been identified as allergic to latex according to their clinical history or a skin test result as the reference method. Performance data (analytical sensitivity, specificity, precision, parallelism) were available in house, but there was and remains today no requirement to submit the performance data for these assays to the FDA. FDA clearance is required only when a manufacturer of a latex-specific IgE antibody assay wishes to sell the product commercially.[29]

FDA-cleared latex-specific IgE in vitro assays

On March 21, 1995, the FDA cleared the first in vitro commercial assay for latex-specific IgE antibody (tube-based AlaSTAT enzyme immunoassay, Diagnostic Products Corporation [DPC], Los Angeles, Calif). The DPC Alastat Microplate (08/15/95), DPC Immulite Assay (11/18/96), Pharmacia CAP System FEIA (12/23/96), and Pharmacia UniCAP FEIA assay (07/03/97) (Pharmaceia, Peapack, NJ) were subsequently cleared by the FDA as being substantially equivalent in their performance to the tube-based AlaSTAT.

In 1999, we compared the diagnostic performance of 3 established FDA-cleared in vitro assays (DPC Microplate Alastat, Pharmacia CAP System FEIA, and the Hycor HYTECH [Hycor Biomedical, Inc., Garden Grove, Calif]) for the detection of NRL–specific IgE antibody.[30] Sera from 117 clinically latex-allergic and 195 clinically nonallergic subjects were obtained from those who participated in the multicenter latex skin testing study.[14] The performance data for these 3 FDA-cleared assays with the history and Greer experimental skin test as reference methods for defining latex allergic cases and controls are displayed in Table II. When the SPT was used as the reference method, the Pharmacia CAP System and DPC Alastat microplate displayed 76% and 73% diagnostic sensitivity, respectively, whereas their diagnostic specificity in comparison with the skin test was 97%. These data indicated that both assays misclassified approximately 25% of latex-sensitized cases as falsely IgE antibody–negative. The HyTECH, in contrast, displayed a specificity of 73%, which indicates that

TABLE II. Performance of FDA-cleared allergen-specific IgE serology tests

Method	Reference	Subjects and mode of classification	Diagnostic sensitivity (%)	Diagnostic specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Efficiency (%)
Pharmacia CAP system*	30	117 Hx+, 195 Hx–	75.2 (67-83)	90.8 (87-94)	83.0 (76-90)	85.9 (81-91)	84.9 (81-89)
Pharmacia CAP system	20	38 Hx+, 44 Hx–	97	86	NA	NA	NA
Pharmacia CAP system*	30	131 SPT+, 181 SPT–	76.3 (69-84)	96.7 (94-99)	94.3 (90-99)	85.0 (80-90)	88.1 (85-92)
Pharmacia CAP system†	31	83 Allergic, 60 nonallergic	79.5	90	91.7	76.1	NA
DPC AlaSTAT*	30	117 Hx+, 195 Hx–	78.6 (71-86)	95.4 (92-98)	91.1 (86-97)	91.1 (84-93)	89.1 (86-93)
DPC AlaSTAT RIA	20	38 Hx+, 44 Hx–	100	33	NA	NA	NA
DPC AlaSTAT*	30	131 SPT+, 181 SPT–	73.3 (66-80)	97.2 (95-99)	95.0 (91-99)	83.4 (78-88)	87.2 (83-91)
DPC AlaSTAT†	31	83 Latex-allergic, 60 latex-nonallergic	74.7	91.7	92.5	72.4	NA
Hycor HyTECH*	30	117 Hx+, 194 Hx–	89.8 (84-95)	67.5 (61-74)	62.5 (55-70)	91.6 (87-92)	75.9 (71-81)
Hycor HyTECH*	30	131 SPT+, 180 SPT–	91.6 (87-96)	73.3 (67-80)	71.4 (65-78)	92.3 (88-97)	81.0 (77-85)

Definitions: diagnostic sensitivity, frequency of a positive latex-specific IgE test result when the individual has latex allergy; diagnostic specificity, frequency of a negative latex specific IgE test result when the individual does not have latex allergy; positive predictive value, percentage of all positive results that are true positives or the frequency of latex allergy in patients with a positive latex-specific IgE antibody test result; negative predictive value: percentage of all negative IgE anti-latex results that are true negatives or the frequency of no latex allergy in patients with a negative latex-specific IgE antibody test result; efficiency, percentage of subjects correctly classified by the latex-specific IgE test as having or not having latex allergy.

NA, Not available; *Hx+,* positive for latex allergy history; *Hx–,* negative for latex allergy history; *SPT+,* positive response to SPT with latex; *SPT–,* negative response to SPT with latex.

*Mean results and (95% confidence limits) are provided from reference 30 using history or puncture skin test with an investigational Greer Skin Test reagent to qualify latex allergic and non-allergic cases.

†Mean results were obtained by using a cutoff value of 0.35 kIUa/L as positive. Subjects were classified as latex-allergic or non–latex-allergic by history and SPT with a home brew natural rubber latex extract.

it produces 27% false-positive results when compared with the skin test. In an independent study,[31] the diagnostic performance of the CAP and Alastat assays were again compared, this time with the use of sera from 83 latex-allergic and 60 nonallergic individuals. Both the CAP and Alastat assays displayed diagnostic performance analogous to those reported previously[30] (Table II) (sensitivity of 79.5% and 73.8% and specificity of 90.2% and 91.7% for the CAP and AlaSTAT assays, respectively). We speculate that the reasons for the low diagnostic sensitivity in the CAP and AlaSTAT assays may be related to poorly represented and/or denatured allergen (eg, Hev b 5) in the allergen-containing reagents used in these assays.[32]

Reproducibility studies have also shown significant imprecision of commercial latex-specific IgE antibody assays at levels close to their positive cutoff values (0.35 to 0.45 kIUa/L),[33] with 35% of the sera producing discordant positive or negative mismatched discrepancies on repeat testing. Another group reported great variation near the positive threshold of the DPC AlaSTAT assay and concluded that latex-specific IgE results from this assay in the 0.35 to 0.7 kIU/L range should be considered equivocal.[34] These studies support the need for duplicate testing when a latex-specific IgE result is a low positive. The authors also suggest that single values, as measured in this range with the microtiter plate–based AlaSTAT ELISA, should not be considered proof of positive latex-specific IgE antibody. In a more recent study, Biagini et al[35] used receiver operating characteristics analyses to define the positive cutoff values that result in maximal diagnostic efficiency for latex-specific IgE as measured in the Pharmacia CAP System, DPC Microplate Alastat, and the Hycor HYTECH assays. This study confirmed that the manufacturer-established positive cutoff value of <0.35 kIU/L produced optimal performance in the Pharmacia CAP and DPC Microplate Alastat assays. However, a positive threshold of 0.11 kIU/L was shown to produce the best assay efficiency in the HYTECH assay.

IN VIVO PROVOCATION TESTING

In vivo provocation can be performed to clarify a patient's actual latex sensitivity status when latex-specific IgE antibody serologic and skin test results are discordant.[36] There are many versions of in vivo provocation tests. Their theoretical advantage rests with their ability to define a relationship between latex allergen exposure and the induction of allergic symptoms in an individual suspected of having a latex allergy. However, provocation test results remain difficult to compare because of the variation among reported protocols in terms of the latex product (glove source and type) used, the duration of rubber product application and subject exposure, and the method used in scoring induced symptoms. Provocation tests can be divided into several groups, which are discussed individually.

Environmental exposure

The most basic form of latex allergen provocation involves the monitoring of patients for allergic symptoms and pulmonary function when they are placed in a latex allergen-containing environment. The performance and interpretation of these provocation tests are complicated by difficulty in accurately quantifying the level of latex allergen levels in the test environment to which the

patient is exposed and quantifying latex-induced allergic symptoms, many of which have subjective end points (eg, itching). To simulate latex allergen exposure, Marcos et al[37] used serial inhalations of an aqueous surgical glove extract. They observed a decline in pulmonary function as measured by spirometry in a patient with latex allergy but not in 2 control subjects; however, conclusions of the study were limited by the small sample size. In another study, Pisati et al[38] exposed 4 individuals with latex allergy to serial dilutions of aqueous extracts from powdered and nonpowdered latex rubber gloves and control cornstarch that had been nebulized into an exposure room. Decreases in pulmonary function as measured by spirometry were observed in all subjects with latex allergy after exposure to powdered latex surgical glove extracts, in 2 subjects after exposure to nonpowdered latex surgical glove extracts, and in none after exposure to an extract of cornstarch powder. The small study population remains a concern in interpretation of these results.

Glove use tests

A number of studies have involved the application of gloves to the hands of patients and observation of their skin after 15 to 60 minutes for the development of erythema, rash, and pruritus, as well as for any nasal and bronchial symptoms. Nonlatex gloves are generally used as controls. In 1991, Heese et al[39] described a glove exposure test for history-positive individuals who had an equivocal or unsatisfactory SPT or patch test response. Their patients were instructed to wear gloves for 2 hours daily on 3 consecutive days. This test has not been easily reproduced by others because the type (powdered, relative allergen content) and source of gloves and their reaction scoring method were not specified. Jaeger et al[28] described a variation on the glove exposure test in which 2 powdered latex gloves (one unwashed and the other washed for 48 hours in saline solution) were concurrently put on the left and right hands of the patient, respectively. Differences in symptoms and skin reactions were noted between the hands with the unwashed latex gloves and those with the washed control latex gloves (theoretically containing no extractable allergen). The authors concluded that their 2-hand provocation test could not differentiate between unwashed test and washed control gloves because identical reactions were observed on both hands of 4 patients with latex allergy, and 6 had stronger reactions on the hand with the washed control glove.

Other investigators attempted to grade the latex allergen exposure by sequentially applying a portion of the glove (a finger or patch) and then a whole glove. In every case, the principal limitation was the subjective nature of their end-point measures and the difficulty in masking the procedure. The allergenic content of latex gloves remains variable, even between lots from the same manufacturer. Intact skin has also proven to be an effective barrier against the transfer and adsorption of latex allergen, making reproducible allergen exposures through the skin difficult to accomplish. To address the issue of skin exposure, we modified the glove provocation procedure to promote allergen introduction into the skin. After the subject donned a vapor mask and goggles to prevent respiratory and ocular exposure, the subject's hands were washed but not dried. A bifurcated needle was then used to puncture the skin through saline solution in 3 places on the volar aspect of both hands. High-allergen powdered latex gloves (Baxter-Allegiance Triflex, Baxter Healthcare Corp., Deerfield, Ill) were then placed on both hands, one of which was covered with a synthetic glove or protective glove liner (Dermapor, WL Gore and Associates, Elkton, Md) to serve as a negative control. Circular pressure was applied by rubbing over the puncture sites 50 times, and the subject was then observed for 30 minutes for any evidence of skin and respiratory symptoms. All 17 of the subjects with positive latex skin test and RAST results experienced localized pruritus with measurable wheals and erythema at the puncture sites on the latex glove–exposed hand but not on the protected control hand. The puncture through saline solution increased the relative sensitivity of the glove use test by abrading the skin. Significant limitations of the procedure remain. Principally among these are the commonly cited difficulties of masking the procedure, quantifying and reproducing a defined latex allergen exposure, and assessing relevant conjunctival and respiratory responses. Finally, the puncture event was viewed as not adding value because the procedure was considered nothing more than a modified skin test.

A second stage was added to the procedure to extend the modified glove provocation to evaluation of respiratory, as well as cutaneous, reactions.[40] The mask and goggles were removed, and the subject was asked to blow up a new powdered latex glove and expel its contents slowly into his or her face. This process was repeated twice, and the subject was observed for 60 minutes for changes in reported symptoms and measured peak expiratory flow rates. In the multicenter skin testing study,[14] this procedure was used to adjudicate discordant latex allergy histories and skin test results. Of the 158 subjects with a positive history of latex sensitivity in the study, 25 had negative latex skin test results. Of these, 24 had a negative 2-stage challenge response and one had a positive 2-stage inhalation challenge response. Moreover, 5 of 180 subjects with a negative history of latex allergy had a positive latex skin test response, and all 5 of these individuals had a negative 2-stage provocation test results. These results indicate either a sensitized but asymptomatic state or a false-positive skin test result. Difficulty in masking the procedure and quantifying and reproducing a defined latex allergen exposure remain limitations of the 2-stage procedure.

Niggemann et al[41] used a modified glove provocation procedure with a glove-wearing and sequential glove inflation test to evaluate latex allergy in children with spina bifida. Children were requested to take their mouths away from the inflated glove when inhaling to prevent inspiration of latex particles. In the 11 children who were too small to cooperate, the glove was turned

inside out and rubbed smoothly on the lips for 1 minute. Fifty-five of the 159 challenged children (62.5% of sensitized patients) had a positive provocation test reaction with local urticaria, in some cases including swelling of the lips. No child had a clinical reaction to the glove inflation test after having had a negative glove-wearing test result.

Laaoprasert et al[42] developed an alternative challenge protocol in which subjects were exposed in an inhalation chamber to increasing levels of allergen through 7 sequential challenges involving the donning and discarding of vinyl, low latex allergen (powder-free), and 5 sets of high latex allergen (powdered) gloves. The subjects' symptom scores and spirometry (FEV_1) were monitored for 60 minutes with each exposure. Each subject wore a laminar flow helmet during all challenges, with a high-efficiency particulate air filter in place only during the first 2 challenges with the powdered high latex allergen gloves. Results of 11 challenges demonstrated that latex allergen levels inside and outside the helmet were not significantly different when vinyl and powder-free gloves were used. A measurable increase in symptom scores and a decline in FEV_1 were observed with the third to fifth powdered latex glove challenge, after removal of the high-efficiency particulate air filter. This challenge procedure reportedly provided a safer and more controlled exposure to latex allergen from powdered latex gloves. It also permitted semi-quantitative measures of latex allergen exposure and symptom end points. Difficulty with masking this provocation method and the added need for an environmental containment chamber were viewed as limitations of the procedure.

Hooded exposure chamber

Kurtz et al[43] reported on a device called the *hooded exposure chamber*, which permits progressive latex aeroallergen exposure to a subject's lower airway, upper airway, and conjunctiva. Latex allergen–associated cornstarch is isolated from powdered latex gloves and diluted serially with untreated cornstarch. The hooded exposure chamber system produces a cloud of latex allergen–associated cornstarch particles (1-10 μm in diameter) with an impinger device that is forced into the hood with an air pump. The subject puts his or her head in the hood and breathes normally as the particulate changes every 18 minutes from no latex allergen (untreated cornstarch as a negative control) to increasing amounts of latex allergen–associated cornstarch particles. An on-line particle laser counter monitors the number of particles and particle size distribution flowing into the hood. Chest and rhinoconjunctival symptom scores, as validated previously,[44] and peak expiratory flow rates are monitored as end points. Cited advantages of the hooded exposure chamber system include the possibility of masking, its inherent safety resulting from the graded aeroallergen exposure, and the generation of quantitative end-point data. Its limitations include the variable potency of the latex allergen–associated cornstarch particulate preparations produced from different sources of powdered latex gloves, the need for specialized and expensive equipment and laboratory space, and the labor-intensive nature and time required to challenge an individual with a series of aeroallergen concentrations.

CONCLUDING REMARKS

As indicated in a recent editorial,[45] ultimate responsibility for the quality of diagnostic testing rests with the referring physician. If a patient has a convincing clinical history of latex allergy and skin testing is selected as the mode of confirmatory testing, then the allergist performing the skin test should ensure that his or her reagents and procedures are validated and traceable to a reference material (eg, NAL [E8] from the FDA). Alternatively, if IgE anti-latex is to be detected by serologic methods, then a federally certified laboratory should be selected, and the assay methods used to measure antibody should either be FDA-cleared or well documented with in-house data. The laboratory selected should also have demonstrated proficiency in the College of American Pathologists Diagnostic Allergy Survey (Northfield, Ill). As a last resort, provocation tests should be performed in those select cases in which a negative skin test or serology result is not consistent with a strong patient history for latex allergy. Care should be taken to ensure safety with graded allergen exposures, to have verifiable latex allergen– containing products that generate measurable allergen exposure, and to use objective measurable end points for defining the outcome of the provocation test.

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